International Journal for Parasitology: Drugs and Drug Resistance 32 (2026) 100669

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

Evolutionary and epidemiological considerations for anthelmintic treatments in ruminant livestock

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ARTICLE INFO

Keywords:
Anthelmintic resistance
Evolutionary epidemiology
Parasite transmission
Model
Gastrointestinal nematode
Ruminant

ABSTRACT

Anthelmintic drug resistance is a concern for the sustained control of gastrointestinal nematodes (GINs) in ruminant livestock globally. Evolutionary-epidemiological modelling, which considers both parasite dynamics and resistance dynamics in response to interventions, can be useful in determining which anthelmintic resistance management (ARM) strategies may be effective without compromising parasite control. We address two key questions in ARM. First, how to improve the measurement of AR in populations. Second, identifying effective ARM strategies to slow the spread of AR while maintaining effective parasite control. We developed a simulation framework which tracks the weather-dependent epidemiology of GINs and AR evolution, providing a highly flexible methodology to evaluate multiple ARM strategy options in a single modelling framework, allowing for novel insights due to direct comparisons between strategies. Simulations to refine our understanding of anthelmintic resistance management evaluated the impact of key areas of uncertainty, including transmission intensity, resistance intensity, resistance frequency, drug decay and linking faecal egg count reduction tests (FECRT) to resistance allele frequency. Large-scale simulations present a methodologically thorough evaluation of how treatment choices simultaneously impact epidemiological and evolutionary outcomes. Phenotypic classifications of resistance status using FECRT failed to capture fine scale changes in resistance allele frequency. The pharmacokinetics of drug decay strongly influenced ARM outcomes, and trade-offs between ARM and effective parasite control depends on genetic factors underpinning resistance. Combination therapies appear to be the most effective resistance management strategy evaluated. Our findings suggest practical implementations to manage anthelmintic resistance must simultaneously consider parasite transmission, pharmacology and parasite genetics to be robust and sustainable. We provide a rigorous simulation framework to enable such discussions allowing for a refinement into our understanding of parasite control in the presence of resistance evolution.

1. Introduction

Chemical control has been widely used to target pathogens, pests and vectors worldwide for decades, leading to the inevitable evolution of resistance (Charlier et al., 2020; Githaka et al., 2022; Rose Vineer et al., 2020). Today, resistance to treatments are some of the most pervasive threats, undermining the sustainability of vector and parasite control in livestock management practices (Charlier et al., 2020; Githaka et al., 2022; Rose Vineer et al., 2020). Resistance management is set of practices (Roush, 1989) intended to delay, slow or mitigate the emergence and spread of resistance that are widely recommended across disease systems (Stubbings et al., 2020; WHO, 2012); and their evaluation is rapidly becoming one of the most urgent challenges in livestock veterinary research.

Mathematical modelling has played a key guiding role in the design and evaluation of resistance management strategies (Bartram et al., 2012a; Rose Vineer, 2020; Tabashnik, 1990). While resistance management strategies used in different systems often share cross-cutting themes, the biological, legislative, operational and economic differences necessitate system-specific models. We focus on anthelmintic resistance (AR) and AR management (ARM) in gastrointestinal nematodes (GINs) of ruminant livestock. AR is estimated to cost the ruminant

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https://doi.org/10.1016/j.ijpddr.2026.100669
Received 29 April 2026; Received in revised form 15 August 2026; Accepted 24 August 2026
Available online 25 August 2026
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livestock industry €38 million annually in Europe (Charlier et al., 2020), a cost that is likely to increase as AR increases. Despite ARM modelling being conducted since the 1980s (Gettinby et al., 1989), there remains uncertainty around the conditions impacting ARM strategy success or failure. Many resistance management claims (REX Consortium, 2013) were neither investigated theoretically nor empirically. For ARM we consider two areas requiring attention. First, how to improve the measurement of AR in populations, and how this is subsequently used to inform strategy choice. Second, identifying effective ARM strategies to slow the spread of AR while maintaining effective parasite control.

The faecal egg count reduction test (FECRT) is a practical, pragmatic measure used to measure anthelmintic treatment efficacy of GINs (Coles et al., 1992). FECRT results can be used to classify GIN populations as "resistant" or "susceptible" using heuristic thresholds from World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines (Kaplan et al., 2023). Recent discussions around FECRTs have focused on the statistical requirements for measurements to inform treatment practices (Denwood et al., 2023), but have not considered the genetics of resistance. Incorrect classification of resistance in populations may lead to incorrect ARM practices.

Transmission intensity, AR genetics and drug pharmacology may concurrently impact parasite control and AR dynamics (Coffeng et al., 2024; Masserey et al., 2022), and it is essential to understand these factors. Areas where GIN transmission is high (due to climate or previous farm management practices) likely have high contamination levels, and therefore a large free-living population in *refugia*, which may itself interact with ARM (van Wyk, 2001) and infection. Models commonly assume a dominance of 0.5 (e.g.,Patel et al., 2024), such that the RS phenotype (heterozygote) is intermediary to the SS (homozygous susceptible) and RR (homozygous resistant) phenotypes. Dominance has important interactions with the decay in treatment efficacy (Hastings, 2001), which may be overlooked as a result. The reduction in the efficacy due to decay has been shown to be an important consideration for both monogenic (South et al., 2020) and polygenic (Hobbs and Hastings, 2025a) resistance. Despite this, the decay in treatment efficacy over time is often a neglected parameter in ARM models. Considering drug decay is most important for treatments with long residual efficacies, such as "newer" anthelmintic formulations (Papadopoulos et al., 2009).

There is a lack of communication between resistance modelling disciplines (Hastings, 2001; Peck, 2001; REX Consortium, 2007) and inevitably, diverse terminologies are used, necessitating individual studies to clarify their terminologies. Unclear and inconsistent terminologies lead to misunderstanding and misinterpretation. To clarify, we consider ARM strategies as the overarching way in which anthelmintic drugs are deployed over space and time. Other aspects such as "*refugia*" or "rotational grazing" are supplementary considerations which may further influence ARM strategy performance. We will discuss the strategies which can generally be placed under the umbrella terms of pharmacological rotations, cohort mosaics and combinations, which we clarify below.

"Rotations" refer to the process of deliberate, pre-planned switches between active ingredients. Synonymously called cycling or alternation, which are also used *ad hoc* (REX Consortium, 2013). For farm livestock management, the term rotation can also be used to describe grazing practices, such as rotational grazing, which is itself a GIN control option (Stromberg and Averbeck, 1999). To distinguish, we use "pharmacological rotations" to describe rotating between different anthelmintic classes. Rotations are suggested as a strategy because resistance to one active can decline while rotated out (Madgwick and Kanitz, 2024).

"Combinations" classically refer to single formulations containing two different active ingredients, which both drugs are effective against the same target species ("narrow spectrum"). The nearest equivalent strategies would be pyramiding for transgenic crops and mixtures for fungicides, herbicides and insecticides. The resistance management rationale of combinations is redundant kill (Curtis, 1985), whereby the dual exposure to two different active ingredients means that even if an individual is resistant to one, they are still likely to be killed by the other partner active ingredient (Madgwick and Kanitz, 2023). For anthelmintics combinations can also refer to "broad spectrum" products, where each active ingredient may be effective against different parasite species.

"Mosaics" refer to the deployment of different active ingredients over space, albeit the spatial scale is not usually further clarified, with spatial scale varying between biological/operational systems. For example, classically in agriculture, mosaics refer to different fields being treated with different pesticides. While for mosquito control, mosaic generally refers to different villages. The term "micro-mosaic" has been used to describe different households in the same village receiving different treatments (Hobbs and Hastings, 2025b). For drug treatments, this could also be at the farm/hospital scale, or at the individual patient level, as each patient acts as its own spatial unit. One option for livestock would be to treat different animals within the same herd with different active ingredients, which we term as a "cohort mosaic".

"*Refugia*" is a common consideration in resistance modelling; including even the very earliest resistance models (Comins, 1977). To put simply, *refugia* is the subset of the population of the target organism which remains unexposed. The use of *refugia* is a considered an anthelmintic resistance management (ARM) strategy (Hodgkinson et al., 2019), but is better considered as an additional component. The term *refugia* in the anthelmintic literature can conflate between "free-living larval *refugia*" and "untreated livestock *refugia*" (Hodgkinson et al., 2019), which both meet the technical definition of *refugia. Refugia* in the anthelmintic resistance literature tends to refer to the "free-living larval *refugia*" (van Wyk, 2001). These distinctions are important considering the ability to measure and quantify the size of each type of *refugia,* and how different types of *refugia* may impact ARM and disease control.

The aim of this manuscript is to provide improved clarity and conceptual guidance for the discussion of ARM by farmers, veterinarians, researchers and policy makers, by extension of the GLOWORM modelling framework (Ingle et al., 2025; Rose et al., 2015; Rose Vineer et al., 2020) to evaluate the implications of various ARM options.

2. Methods

2.1. Model overview

We extend the GLOWORM simulation framework, which in brief, is a GIN transmission model which captures the lifecycle of GIN infecting ruminant livestock and encompasses the free-living (Rose et al., 2015) and parasitic (Rose Vineer et al., 2020) life stages of the GINs. The model has been further extended to simulate parasite metapopulations, comprising sub-populations on separate patches (fields within a farm) (Ingle et al., 2025), the META extension. We further extend this by including livestock metapopulations (COHORT extension) and resistance genetics, as either a single-gene (AR extension) or two-gene (AR2 extension). The technical detail is fully described in the supplementary file (Section S1) but given as a conceptual overview here. The conceptual modularisation and extension of the GLOWORM framework is presented in Fig. 1. Full model code and simulation output are provided in a Figshare repository (Hobbs and Rose Vineer, 2026).

The COHORT extension duplicates the in-host equations, so that each cohort has its own set of equations, which links pasture subpopulations by ingestion of the L3 (infection) and excretion of eggs in faeces (contamination). Each cohort can be given unique properties such as age, patch movements or treatments. For the AR and AR2 extensions, each genotype permutation is tracked individually for each life stage of the GIN, in each patch and cohort. This allows for treatments to have unique impacts against each genotype. The assumption of monogenic resistance is widespread throughout the resistance modelling literature regardless of biological system (e.g., Helps et al., 2020; Levick et al., 2017; Madgwick and Kanitz, 2022; Reichert et al., 2023; REX

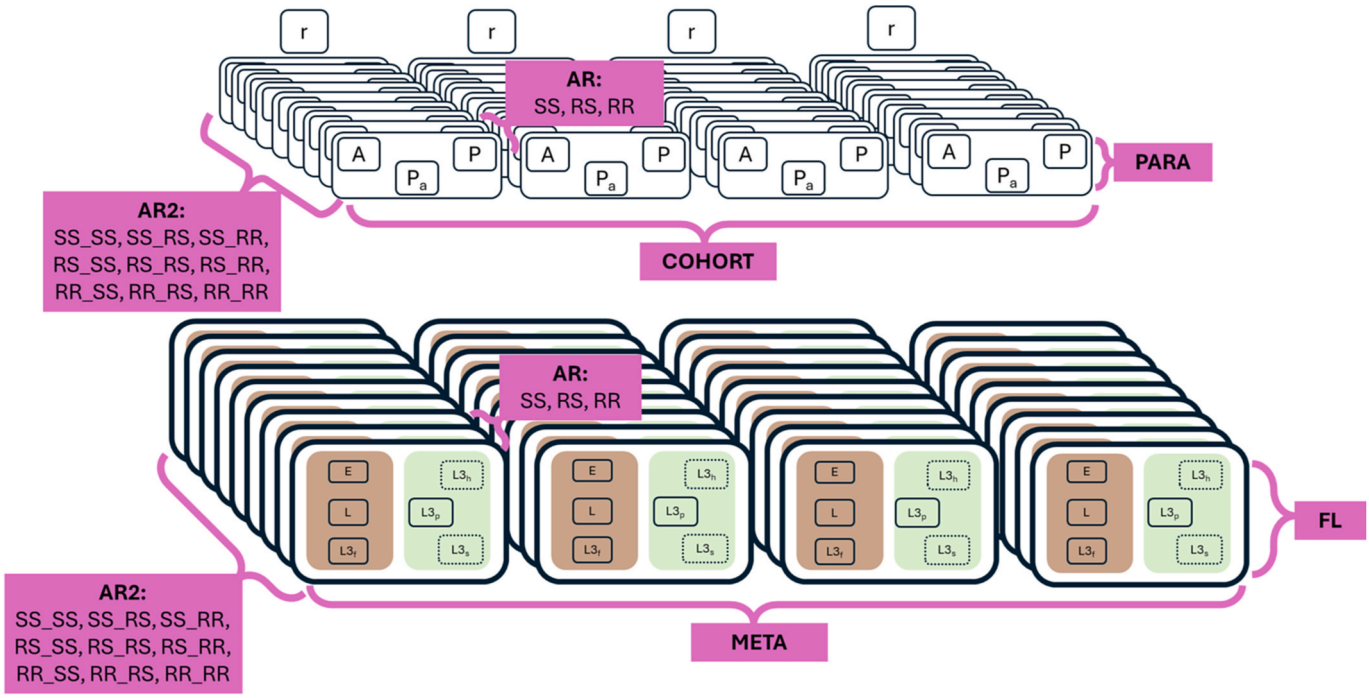


Fig. 1. GLOWORM-META-COHORT-{AR, AR2} Modularisation. The GLOWORM model framework consists of a modular format, allowing for the different extensions to be used in unique permutations. The FL (lower half of diagram) (Rose et al., 2015) and PARA (upper half of diagram) (Rose Vineer et al., 2020) are the core parasite transmission components of the model, used across all other model extensions. The META (Ingle et al., 2025) component extends to allow for separate patches for free-living parasites (represented by replication from left to right of the lower half of the diagram). The new COHORT extension allows for separate groups of grazing livestock (represented by replication from left to right in the upper half of the diagram). The AR and AR2 extensions are when the number of different anthelmintic genes being tracked is specified (represented by replication from front to back of the diagram, on the z axis).

Consortium, 2013), and is consistent with single nucleotide polymorphisms conferring resistance to benzimidazoles and levamisole (Doyle et al., 2022). This approach can also represent more complex multiple co-selected and linked genomic regions conferring resistance, as may be the case for ivermectin resistance, for example (McIntyre et al., 2025).

The addition of the COHORT and AR/AR2 extensions to the GLOWORM framework, allows for an increase in the number, variety and complexity of ARM strategies that can be investigated, some demonstrations of the updated model capability are in the supplementary file (see Section S4). Model validation is conducted against previously published data (Sargison et al., 2012; Stear et al., 2006; Waller and Thomas, 1975), and is detailed in the Supplementary File (Section S5).

2.2. Simulation sets

We consider three simulation sets, which each have a different focus.

- Simulation Set 1: Resistance classification and linking FECRT to resistance frequency and treatment efficacy
- Simulation Set 2: Impact of genetic and drug efficacy properties on parasite control and resistance spread.
- Simulation Set 3: Evaluating strategies for parasite control and managing resistance.

The GLOWORM simulation framework has a large degree of capability and flexibility (Fig. 1); running these sets separately allows for the specific aspects to be investigated in isolation, providing better mechanistic understanding than if all features were investigated simultaneously. For all our presented simulations we use the GLOWORM model with the *Haemonchus contortus* parameterisation (Rose et al., 2015), this is fully detailed in the model code in the "*gin*" function. As we are using the model and reporting the results in highly generalisable ways, the high-level results (e.g., directionality and ranking of strategies) are likely to be qualitatively applicable to any GIN species in any livestock species. Given drug formulations vary in efficacy depending on the livestock breed (Gotardo et al., 2020; Hosking et al., 2010), parasite species, and exact formulation/method of application (Garg et al., 2007), we are also agnostic with regards to the specific anthelmintic deployed, but explore different characteristics which are detailed later. The generalisable performance of different ARM options to understand the evolutionary and epidemiological implications has the added benefit of results being broadly applicable to potential "new" anthelmintics for which pharmacokinetics, spectrum of activity and genetic mechanisms of resistance are unknown. In all simulations, resistance allele frequencies in the adult GIN population are initiated in Hardy-Weinberg equilibrium ($R^2 + 2RS + S^2 = 1$) for both within-host and free-living stages.

We consider livestock (sheep) reared at a stocking rate of ten per hectare (equivalent to 1 livestock unit (Eurostat, n.d.)). The livestock remain at a fixed weight of 65 kg. We consider only single-patch simulations (not using the META extension), where sheep remain on the same pasture throughout the simulations (there is no rotational grazing), because this ensures the impact of the cohort *refugia* and larval *refugia* can be better isolated and investigated explicitly. Location-specific precipitation and temperature were extracted with the *openmeteo* R package (Pisel, 2023).

2.2.1. Simulation set 1 design: resistance classification and linking FECRT to resistance frequency and treatment efficacy

Simulation Set 1 considers how observed drug efficacy, from FECRTs, translates to the GIN resistance allele frequency. FECRT is calculated given the input resistance allele frequency, the genotype, drug parasite kill rate and dominance. Simulations only need to be of a short duration (10-days) to cover the treatment period, and the impact of climate can be ignored. Simulations are run for a single anthelmintic,

to align with current WAAVP guidelines (Kaplan et al., 2023) which do not consider combination therapies.

We vary the following parameters:

- *Drug efficacy*: This is the parasite kill rate against the SS genotype. We consider the drug efficacy values of 1, 0.999, 0.99, 0.98, 0.95, 0.9. Where a value of 1 indicates all SS genotypes are killed.
- *Resistance intensity*: This is the parasite kill rate against the RR genotype. We consider resistance intensity values of 0, 0.001, 0.01, 0.02, 0.05, 0.1. Where a value of 0 indicates no RR genotypes are killed.
- *Dominance*: We consider the dominance of resistance, which describes the RS phenotype in relation to the SS and RR phenotypes. Where a dominance of 0 indicates the RS phenotype is the same as the SS phenotype, and a dominance of 1 indicates the RS phenotype is the same as the RR phenotype. We explore all values between 0 and 1 at 0.05 intervals.
- *Resistance frequency*: This is the frequency of the R allele in the population. We explore all values between 0 and 1 at 0.01 intervals.

To clarify, resistance intensity describes the level of resistance the RR genotype provides, while resistance frequency is the occurrence of the resistance allele in the population. GIN populations could have frequent but low intensity resistance or, conversely, infrequent but intense resistance.

The parameter space described above gives a total of 76,356 unique parameter permutations. For simplicity, we assume the drug has an instantaneous effect on reducing the adult worm burden by the specified level given the genotype, and that there is no drug decay. The outcome extracted from each simulation permutation is the FEC on day 1 (pre-treatment) and day 10 (post-treatment), which is used to calculate the FECRT. The exact FECRT is reported for each simulation permutation. We further classify simulated populations as "resistant" or "susceptible", considering various thresholds which are or have been used or proposed: 95%, 90% and 80% (Coles et al., 1992; Kaplan et al., 2023), to demonstrate how changing threshold impacts the classification of population.

2.2.2. Methods common to simulation sets 2 and 3

Simulation sets 2 and 3 concern the deployment of anthelmintic drugs over multiple years. Each simulation is three years in duration, starting 01/01/2018 and ending 31/12/2020 from 100 randomly sampled locations in the UK to account for weather variability. Simulations start with a 1-year "burn-in" to establish the desired conditions for the subsequent years (i.e., suitable pasture contamination levels and immunity). No anthelmintic treatments are given during the burn-in period, and the burn-in is not included in the analysis. The burn-in generates two generalised transmission intensity settings of "lower" and "higher" for each location. Here, transmission intensity corresponds to the level of pasture contamination that would on average (across all locations) give a peak FEC of 1250 to 1500 ("higher" transmission) and 750 to 1000 ("lower" transmission) in the second year in the absence of drug treatments. Transmission intensity calibration details are presented in the supplementary file (Section S2, Figure S2.1).

From the simulations we extract the following outcomes:

a) the FEC in each cohort and the whole population as a measure of parasitism,
b) L3 (infectious larval stage) pasture count as a measure of transmission intensity,
c) resistance allele frequency in the L3 on pasture, as a measure of ARM.

2.2.3. Simulation set 2 design: impact of genetic and drug efficacy properties on parasite control and resistance spread

Simulation Set 2 explores the implication of parameters concerning refugia size, transmission intensity, drug decay, resistance allele frequency, drug efficacy, resistance intensity and dominance on the spread of drug resistance and their interaction with parasite control. These parameters are frequently highlighted as important considerations (REX Consortium, 2013), albeit under-investigated in the veterinary GIN context. We consider treatments with a single active ingredient to focus on the mechanistic understanding in relation to these parameters. Anthelmintic treatments are given on day 100 of years 2 and 3 of the simulation to the livestock in Cohort 1 (the treatment cohort) irrespective of the worm burden. Cohort 2 (the *refugia* cohort) never receives any drug treatment. The anthelmintic drug targets only the adult life stage of the GIN. All possible permutations were used (288 permutations) and replicated across the 100 locations (28,800 simulations). The parameters explored were:

- *Refugia size*: "Untreated livestock *refugia*", such as achieved through targeted selective treatment (TST) (Gaba et al., 2010); is implemented by dividing the sheep into two cohorts which co-graze the same pasture and differ only in the anthelmintic treatments given. The stocking rate of cohort 1 ("treatment cohort") and cohort 2 ("*refugia* cohort") therefore sums to ten. We investigate TST by withholding the drug treatments from 0, 10 or 20% of the livestock population, which describes the relative sizes of the treatment and *refugia* (untreated) cohorts. Only Cohort 1 ("treatment cohort") receives anthelmintic treatments.
- *Transmission intensity:* higher and lower as previously detailed.
- *Drug decay*: We consider an anthelmintic treatment of a single active ingredient with the general properties of having an effective duration of four weeks (28 days) after which drug decay either is present or absent. Details of the inclusion are in section S2 of the Supplementary file. A visual representation is in Fig. 2.
- *Resistance frequency (allele frequency):* The starting resistance allele frequency is 0.01 (1%) or 0.1 (10%) in the simulations.
- *Drug Efficacy*: parasite killing efficacy against the SS genotype of 99 or 90%
- *Resistance Intensity*: The initial parasite killing efficacy against the RR genotype of 1 or 10%.
- *Dominance*: The initial parasite killing efficacy against the RS genotype depends on the RR and SS phenotypes and dominance, which was investigated considering dominance to be 0.25, 0.5 or 0.75.

2.2.4. Simulation set 3 design: evaluating strategies for parasite control and managing resistance

The purpose of simulation set 3 is to consider the deployment of different active ingredients (e.g., drug classes) as part of rotational, mosaic or combination ARM strategies over space and time, and evaluate their comparative performances/effectiveness (evolutionary and epidemiological), to identify broad recommendations of how to better deploy anthelmintics. We consider the deployment of two anthelmintic drugs (A and B), where resistance to each drug is encoded by a single gene. The anthelmintics differ in their mode of action, with no cross resistance or cross selection. Treatments are given monthly from February 1st to July 1st (six treatments) in years two and three. Each drug treatment has a residual duration of one week with no efficacy decay. Each round of treatment covers 80% of the livestock population. We evaluate a total of nine different ARM strategies. The parasite kill rates against each genotype to each drug were: 0.95 (RR), 0.5 (RS) and 0.05 (SS), dominance is 0.5. We consider only the "higher" transmission parameterisation previously detailed.

Further to the broad definitions given in the introduction, rotations, mosaics and combinations are interpreted for ARM simulations as follows:

Pharmacological rotations: The frequent rotation of active ingredients has often been recommended as a generalisable resistance management strategy (WHO, 2012) to prevent reliance on a single active ingredient. Although ARM guidance is shifting away from this generalisable recommendation to more farm-specific recommendations (Stubbings

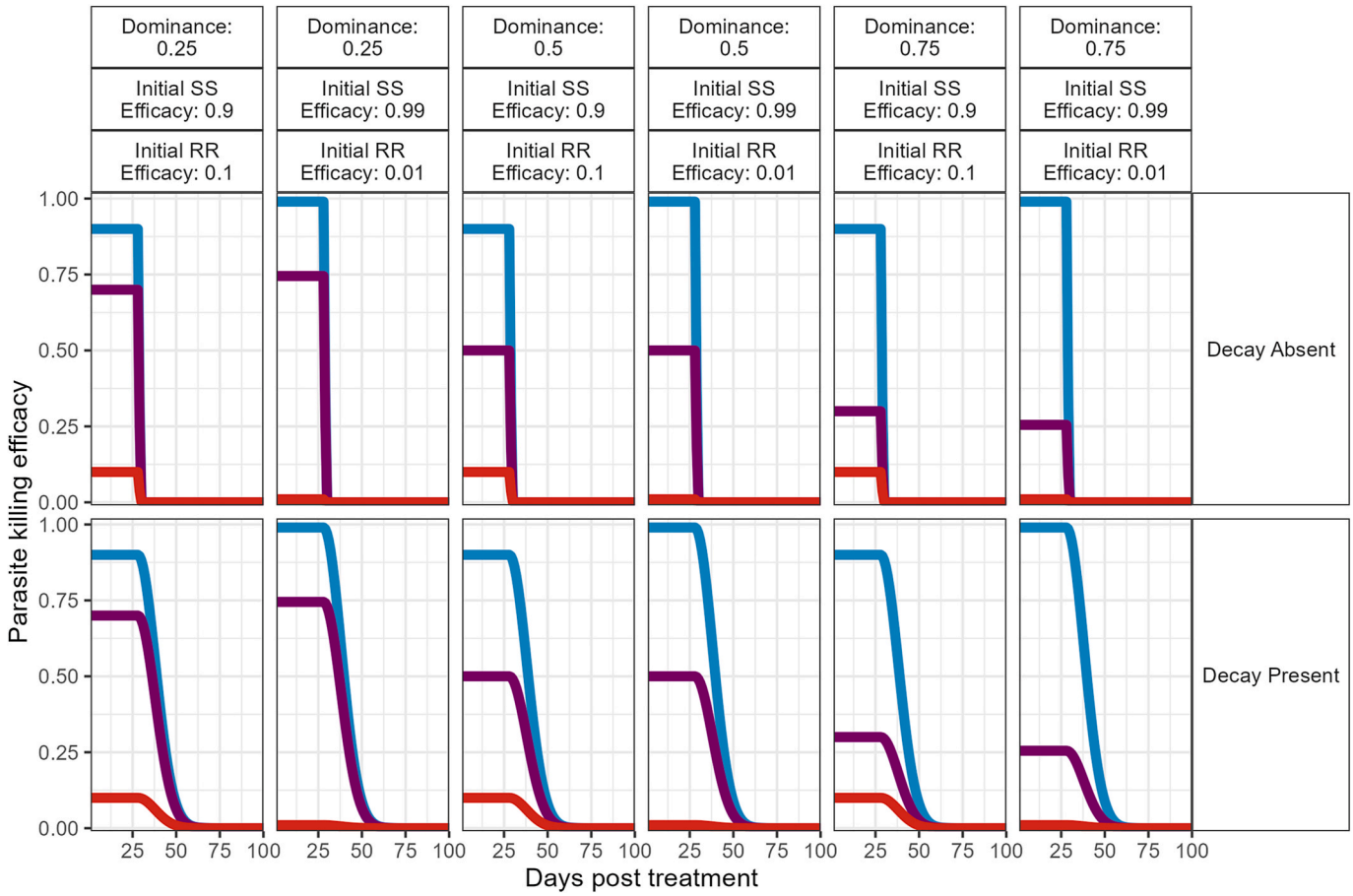


Fig. 2. Anthelminthic drug decay profiles used in the simulations. Plot shows the drug efficacy (parasite killing) for various drug decay profiles and resistance genetic situations. In each plot, the line colours are the parasite killing efficacy over time for the SS (blue), RS (purple) and RR (red) genotypes. The panel descriptions to the right indicate how drug decay is implemented. The top panels describe the parasite genetics and resistance status, such that the top row is dominance, middle is the initial (at treatment) efficacy to the SS genotype, and the bottom row descriptor is the initial (at treatment) efficacy to the RR genotype. The y axis describes the time since treatment, that is the number of days since the drug treatment was given, where day 1 is the day treatment is given.

et al., 2020), in the absence of farm-level data, rotations may be defaulted to for ARM.

Mosaics: Mosaic strategies involve deploying different interventions in different locations. The mosaic term is agnostic to spatial scale, which may have different impacts. For pesticide/herbicide applications mosaics could be at the farm, field or row scale. For anthelmintics in livestock we can consider the "landscape" to be the field the livestock animals are grazing on, or when considering landscape from the GIN perspective each individual livestock animal is itself a component of the mosaic. We therefore distinguish these as "paddock mosaics" and "cohort mosaics". We do not investigate "paddock mosaics" further. For "cohort mosaics" we can further consider how treatments are given to the cohorts over time. In all scenarios, both cohorts co-graze the same patch (pasture). We acknowledge cohort mosaics are likely challenging to implement logistically.

Combinations: both drugs (A and B) are administered simultaneously as a single drug formulation, where each drug is given at their recommended therapeutic dose. We assume (as is a common assumption, e.g. Curtis, 1985; Hobbs and Hastings, 2025b; Madgwick and Kanitz, 2022; Mani, 1985) that survival is multiplicative with drug combinations. For example, the RR_RR survival probability would be 0.95 (drug A) * 0.95 (drug B), which is 0.9025. And for the SS_SS genotype would be 0.05 (drug A) * 0.05 (drug B), which is 0.0025 (see Figure S3.1 in Section 3 of the Supplementary File). The parasite kill rate is therefore one minus the survival probability. To account for the expected higher financial costs of combinations (as each treatment contains two active ingredients), we also consider two potential compromises (assuming drug dose is not compromised) regarding treatment coverage and frequency.

The parameters explored were:

- *Resistance frequency:* Each drug (A and B) can have a starting resistance allele frequency: 10^{-6}, 0.01, 0.1 or 0.25; and all permutations are explored. We explored a wider range of resistance frequencies to allow for a better understanding of how using two different drugs with different initial frequencies influences ARM performance.

The strategies evaluated were:

- Monotherapy: a single anthelmintic (drug A) is given during each treatment event. This acts as the baseline non-strategy comparator.
- Monthly pharmacological rotation: the drugs (A and B) are alternated at each treatment event.
- Yearly pharmacological rotation: the drugs (A and B) are alternated yearly. Such that all treatments in year 2 are with drug A, and all treatments in year 3 are with drug B.
- Fixed cohort mosaic: Livestock receiving treatment are assigned to either to cohort 1 or cohort 2. Cohort 1 receives drug A for each treatment. Cohort 2 receives drug B for each treatment.
- Monthly rotation cohort mosaic: Livestock receiving treatment are assigned to either to cohort 1 or cohort 2. Cohort 1 receives drug A for the first treatment, then rotating between drugs A and B at each treatment. Whereas Cohort 2 receives drug B for the first treatment, then rotating between drugs A and B at each treatment. Cohort 1 and 2 never receive the same drugs at the same treatment.

- Yearly rotation cohort mosaic: the yearly rotation equivalent to the monthly rotation cohort mosaic described above.
- Combinations: where both drug A and drug B are combined in a single formulation and livestock therefore receive both drugs simultaneously.
- Combinations with reduced coverage: Each round of treatment covers 70% of the livestock population.
- Combinations with reduced frequency: Only 5 treatments are given each year, the July 1st treatment (the last treatment of the year) is not given.

This generates a total of 144 resistance-strategy permutations which are run over 100 geographic locations to account for the impact of climate on GIN population dynamics (total n = 14,400 simulations).

We report the percentage differences in the outcome measures when compared against the baseline monotherapy deployment for each timestep (t):

$$\%\ Difference\ (t) = \left(\frac{(Outcome_{strategy\ (t)} - Outcome_{monotherapy\ (t)})}{Outcome_{monotherapy\ (t)}}\right) * 100$$

Therefore, when the $\%\ Difference(t)$ is positive this indicates the monotherapy performed better, and when the $\%\ Difference(t)$ is negative the comparator strategy performed better when evaluating for the specified outcome measure. The overall performance of any strategy is the composite of these differences across all outcomes, however where the challenge comes is in weighting the outcomes against each other, and their importance depends on the time horizon and priority of the strategy in question.

3. Results

3.1. Simulation set 1 results: resistance classification and linking FECRT to resistance frequency and treatment efficacy

Fig. 3 (left-hand plot) shows the classification of GIN populations based on FECRT, when considering a range of resistance frequencies, resistance intensities and dominance alongside some pre-defined thresholds which constitute the target GIN population is resistant or susceptible. The right-hand plot of Fig. 3 conversely reports the corresponding exact FECRT results, providing a more nuanced picture on how resistant the target GIN populations are.

Phenotypic classification varied with dominance; increasing the dominance of resistance alleles in heterozygotes resulted in phenotypic population classifications of resistance at a lower resistance allele frequency (Fig. 3, left panels), thus, knowledge of the dominance of resistance alleles is required to infer resistance phenotype from molecular investigations. Likewise, where resistance phenotype and allele frequency are known, inference can be made regarding possible dominance.

Where dominance is low and drug efficacy against homozygote susceptible GINs is high, phenotypic measures of resistance (FECRT) did not meet the threshold for classification of resistance until resistance allele frequencies were as high as 25%, even under the most conservative threshold of 95% FECRT (Fig. 3, bottom left panels).

3.2. Simulation set 2 results: impact of genetic and drug efficacy properties on parasite control and resistance spread

Increasing the proportion of the in-host parasitic stages *in refugia* by increasing the proportion of livestock left untreated (the different coloured lines in Fig. 4) increases the overall FEC compared with the baseline of whole-group treatment (0% left untreated). In subsequent

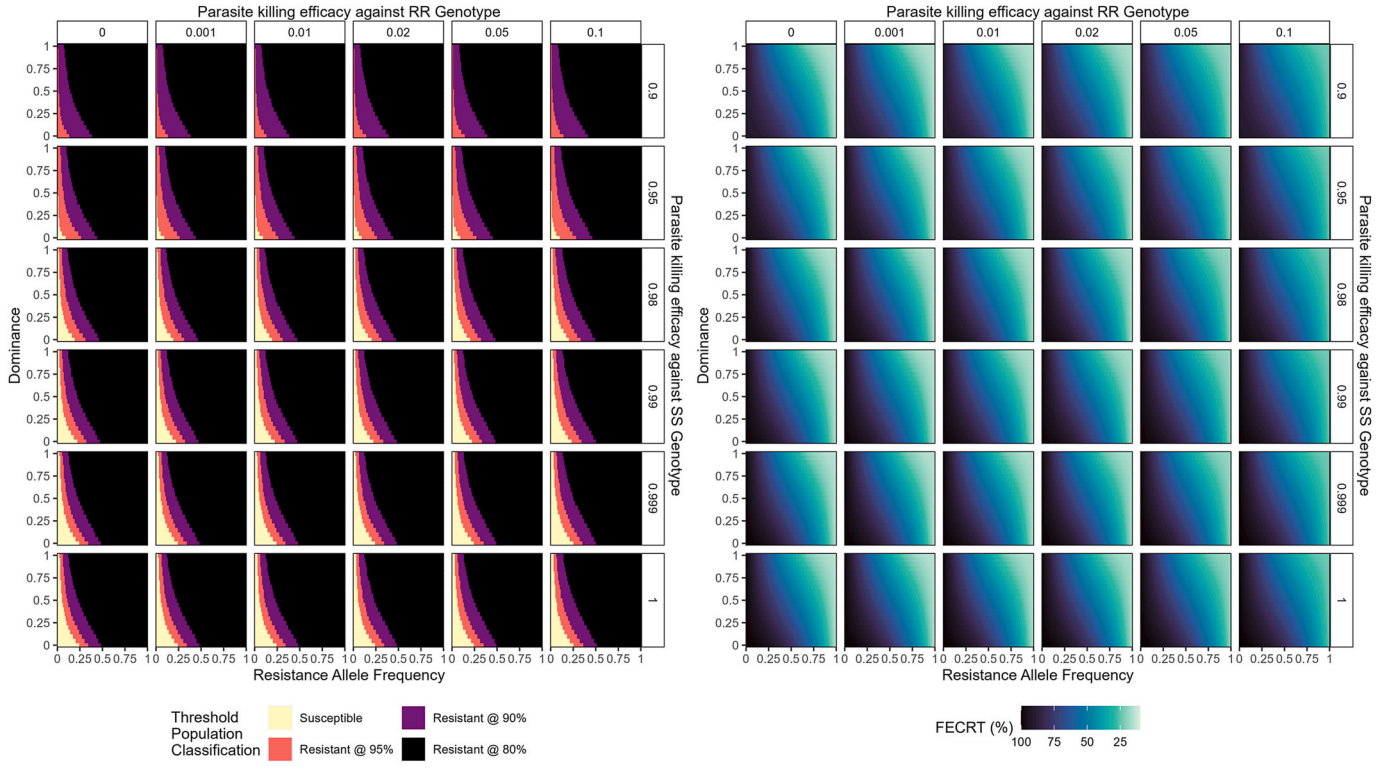


Fig. 3. Faecal Egg Count Reduction Test given Drug Efficacy and Resistance. Both panels share the same overarching format: the resistance allele frequency is the x-axis, the dominance of resistance is the y-axis, the parasite killing efficacy against the RR genotype is represented by panels from left-right; and the parasite killing efficacy against the SS genotype is represented by panels from top-bottom. The left-hand plot shows the FECRT resistance categorisation assuming various threshold faecal egg count reduction percentages (Coles et al., 1992).

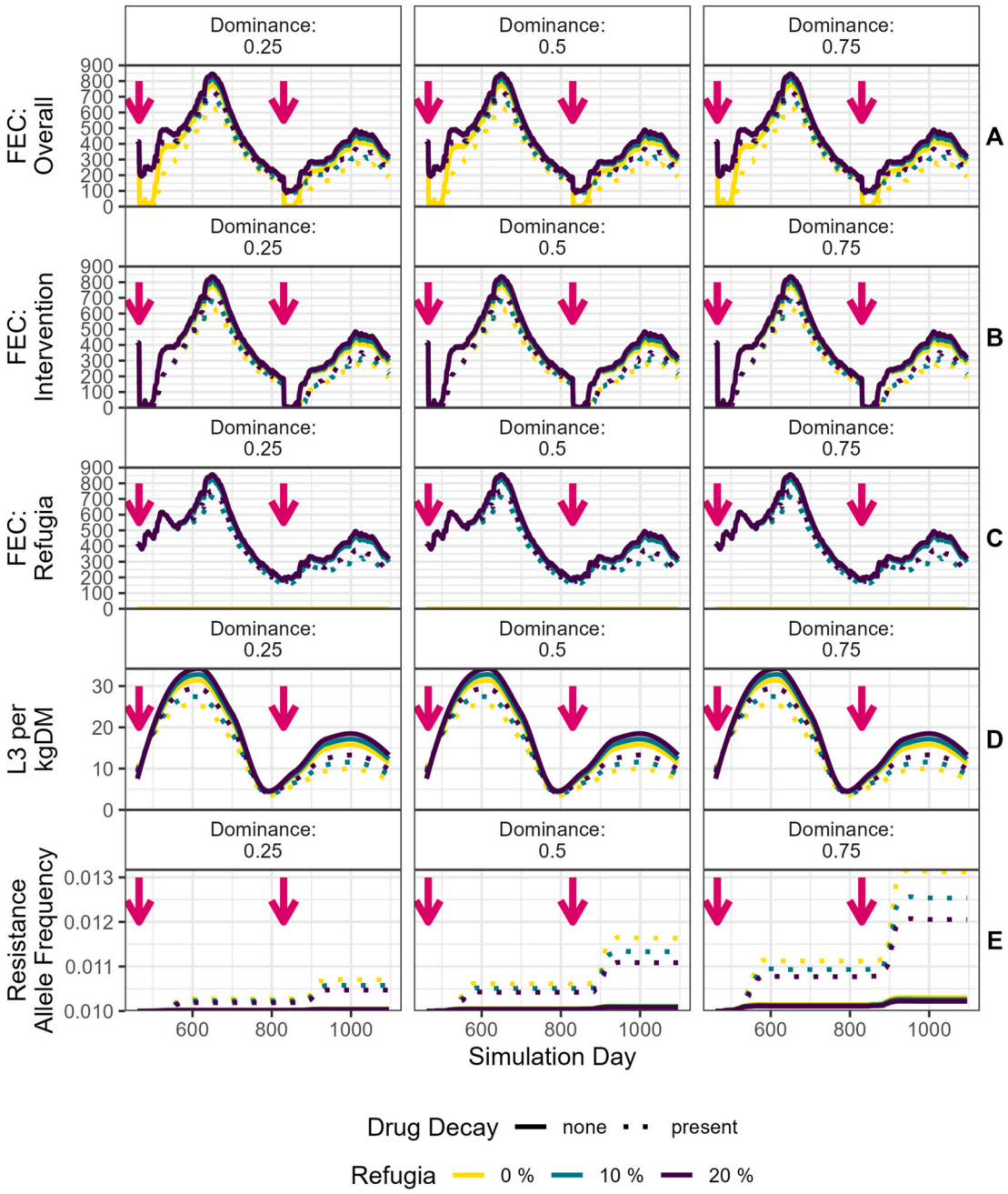


Fig. 4. Results for Simulation Set 2: Influence of parameters on transmission and resistance. In all panels the colour of the lines indicates the proportion of the total livestock population that is untreated (*refugia*), from 0% (yellow) to 10% (green) and 20% (purple). The line type indicates whether drug decay was not (solid line) or was (dashed line) included in the simulations. The top row (A) shows the mean faecal egg count for the whole livestock population (treated and untreated), and is the mean value from the 100 geographic locations. The second row (B) shows just the mean value for the treated cohort, and the third (middle) row of plots (C) shows the mean FEC for untreated cohort (*refugia* population). The fourth row (D) shows the smooth mean value (using loess smoothing) for the L3 larval densities on pasture. The bottom row (E) shows the change in the resistance allele frequency over time. Plots are restricted to only showing years 2 and 3 of the simulation as year 1 is used as burn-in to seed the simulation. The pink arrows indicate the days the drug treatments are administered. The plots are stratified left-right by dominance. Only initial genotype frequencies of SS = 0.9 and RR = 0.1, and the higher transmission settings are shown in this plot, the full results are displayed in the Supplementary File (Section S3), but importantly do not alter the qualitative conclusions which can be drawn.

years, this results in a similarly elevated larval pasture count compared with baseline, and therefore subsequent transmission intensities are higher. The benefit of maximising *refugia,* though, is demonstrated in the simulations as slowing the increase in resistance intensity (allele frequency), and this effect can be considerable when also considering drug decay.

Including drug decay (the dashed lines in Fig. 4) has the short-term epidemiological benefit of treatment being improved (as the killing time is extended, even if diminished, as shown by the dashed lines in the FEC plots in Fig. 4 being lower than the comparator solid lines where drug decay was not included). Second, but far more importantly, is that this benefit is offset by the drug decay tails increasing selection for resistance, see the bottom panels of Fig. 4 where the dashed lines (decay present) are notably higher than when drug decay was not included). The impact of drug decay on the development of resistance, as demonstrated by changes in resistance alleles over time, was also positively

influenced by the predicted dominance of resistance alleles in heterozygotes, with higher dominance levels associated with substantial differences between simulations with and without decay.

Exploring the impact of transmission intensity and initial frequency of resistance (Figures S2.3 to S2.7) show that there remains a similar pattern. However, we note that in higher transmission settings the prespecified treatment plan may not be sufficient to adequately control parasites and so treatment number would perhaps need increasing to compensate for this.

3.3. Simulation set 3 results: evaluating strategies for parasite control and managing resistance

Figs. 5 and 6 show the results for the simulations directly evaluating ARM strategies. To aid reading between all the plots, the colour scheme and plot layout is consistent between all plots and differ only in the outcome being evaluated (Fig. 5 is FEC, and Fig. 6 is resistance allele frequency).

The effectiveness of simulated ARMs in reducing FEC, was highly dependent on the initial resistance allele frequency for both drugs. When resistance to the monotherapy drug (drug A) was lower than drug B the ability for alternative strategies to suppress FECs was often impaired (Fig. 5), highlighting that using the most effective anthelmintic treatment for parasite control is recommended. When drug B had lower initial resistance than drug A (e.g. a scenario where a "new" anthelmintic is used in rotation with an "older" anthelmintic) using strategies that had both drugs in use was generally beneficial in reducing FEC (Fig. 5). When initial resistance allele frequency to each drug was equal, then strategies that used both drugs were beneficial, except the combinations that had either reduced coverage or reduced frequency. Although it should be noted, the absolute differences in FECs were not that different (Figure S3.2 in the Supplementary File).

When considering the impact on resistance, all strategies were found to be better than monotherapies, except for reduced coverage and reduced frequency combinations when resistance was very low (Fig. 6); this is because reduced coverage and reduced frequency kills fewer worms, reducing the dilution benefit from L3 *in refugia* on pasture. Combination therapy outperformed all other strategies from a resistance management perspective, especially when no constraints are applied. Cohort mosaics performed well from a parasite control perspective (Fig. 5), consistently reducing FECs compared with baseline monotherapy. While the combination therapies did not necessarily outperform other strategies epidemiologically (when looking at FEC, Fig. 5), the performance of combinations when considering resistance management was generally better than other strategies (Fig. 6). This is an issue which would unlikely be considered in clinical trials or in the development of clinical guidelines focussing on measures of intensity of infection (FECs) as their outcome of interest.

4. Discussion

We presented results from an extended GLOWORM model framework, which included AR genetics and host cohorts, providing a novel evolutionary-epidemiological modelling framework for GIN control in ruminant livestock. These results provide avenues for a refined, high-level discussion regarding ARM and interpretation of molecular studies of AR. When considering evolutionary-epidemiological dynamics with respect to ARM, there are two outcomes of interest which are often in conflict: parasite control and resistance management. ARM guidelines need to provide practical and actionable recommendations without compromising parasite control, livestock welfare and productivity, and input costs (Learmount et al., 2015).

While short-term epidemiological dynamics are readily observable in trials (e.g., Little et al., 2010), the longer-term evolutionary dynamics of AR are often less tractable. This is in part because trials are focused primarily on whether an intervention is effective in the moment, because resistance management strategies cannot be considered if they fail at the primary task of reducing the immediate parasite/transmission burden, and due to the lack of genetic markers for resistance for some anthelmintic classes (McIntyre et al., 2025). Evolutionary-epidemiological models can be used to make qualitative statements regarding the comparative performance of strategy options, and to generate broad guiding principles behind resistance management.

Our simulations suggest: that resistance phenotype is an imperfect measure of resistance allele frequency; that pharmacokinetics (specifically residual activity) strongly influences the outcome of ARM; and that the balance between long-term ARM and effective parasite control in the short-term depends on genetic factors underpinning resistance within these parasite populations. We made two notable assumptions in our modelling approach.

First, our simulations gave treatments at set times regardless of the level of parasitism experience by the livestock. Strategies which perform worse at clearing parasitic infections may require repeated treatments selecting further for resistance; and similarly increased transmission would lead to re-infection and therefore the need to re-treat; which explains our findings that transmission intensity had minimal impact on resistance propagation.

Second, we assumed resistance to be monogenic, a common assumption across a range of models and diseases (Barbosa et al., 2018; Helps et al., 2020; Madgwick and Kanitz, 2022; Patel et al., 2024; Reichert et al., 2023; REX Consortium, 2013). Where models assume polygenic resistance (Coffeng et al., 2024; Hobbs et al., 2023; Hobbs and Hastings, 2025b) they give qualitatively similar results to their monogenic equivalents (Levick et al., 2017; South and Hastings, 2018) regarding strategy evaluation, which gives confidence that assumptions regarding the genetics of resistance do not drastically alter the qualitative performance of resistance management strategies, although the magnitudes of benefit may differ.

We demonstrated how minor changes in resistance intensity (the level of resistance from the RR genotype), dominance and resistance frequency can change whether a population would be categorised as resistant based on established thresholds (Fig. 2, left panel), masking far less drastic changes in anthelmintic efficacy (Fig. 2, right panel). This challenges the tendency for practitioners, policy makers and scientists to apply thresholds to a quantitative continuum and classify whole populations as resistant or susceptible. Although this is useful for prompting early farmer behaviour change in favour of ARM strategies, the variability in potential resistance allele frequency at these resistance thresholds, as shown in our simulations, may undermine ARM strategies reliant on a "low" initial resistance allele frequency (Bartram et al., 2012b). With an increase in modelling resistance as a quantitative trait (Coffeng et al., 2024; Hobbs and Hastings, 2025b), the communication of resistance as a continuum of phenotypes is starting to make headway. Without these more refined considerations of what the "resistance" problem is, assessing it becomes challenging.

Considering the importance of drug decay in impacting resistance dynamics in other systems (Stepniewska and White, 2008), failures to include drug decay may mean we are not fully understanding ARM strategy performance. Of note is the importance of dominance and drug decay. High levels of dominance combined with drug decay hugely increases the change in the resistance allele frequency; these are two parameters not widely investigated and the effect of them appears to be as influential as the inclusion of *refugia* in influencing resistance dynamics. Thus, inclusion of drug decay in cost-benefit analyses is essential.

Of note is that, when dominance is high and drug decay is included, this leads to a situation allowing for rapid spread of resistance. This is an especially important consideration, as many new anthelmintic drug formulations are intended to have long efficacy durations, meaning there is ample time for the drug to decline in concentration. We also assume there are no mistakes made in dose of the anthelmintics given, which would be most likely be due to underdosing in a practical setting.

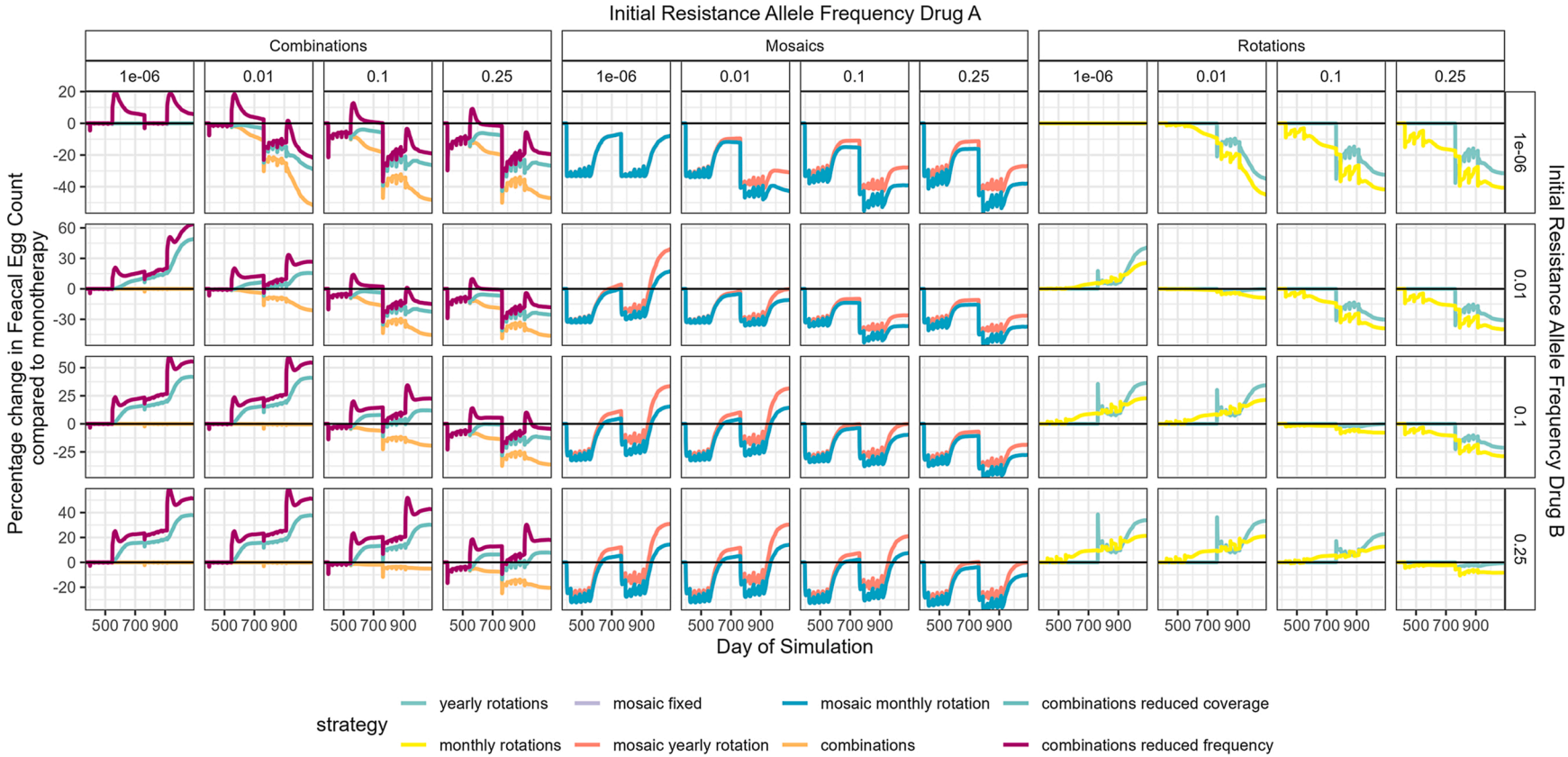


Fig. 5. Simulation Set 3 – Percentage Difference in the Faecal Egg Count Compared to Monotherapy. The y axis is the percentage difference, as calculated from Equation (1). The horizontal black line (at zero) represents no difference between strategies. Values below the black line indicate the proposed strategy performed better, and values above performed worse than the Monotherapy comparator. The colour of the lines indicates the specific strategy. The x-axis is the simulation day and is restricted to not include the 1-year burn-in, which is the same across all strategies. Each line is the mean of 100 simulations, covering a range of geographic locations.

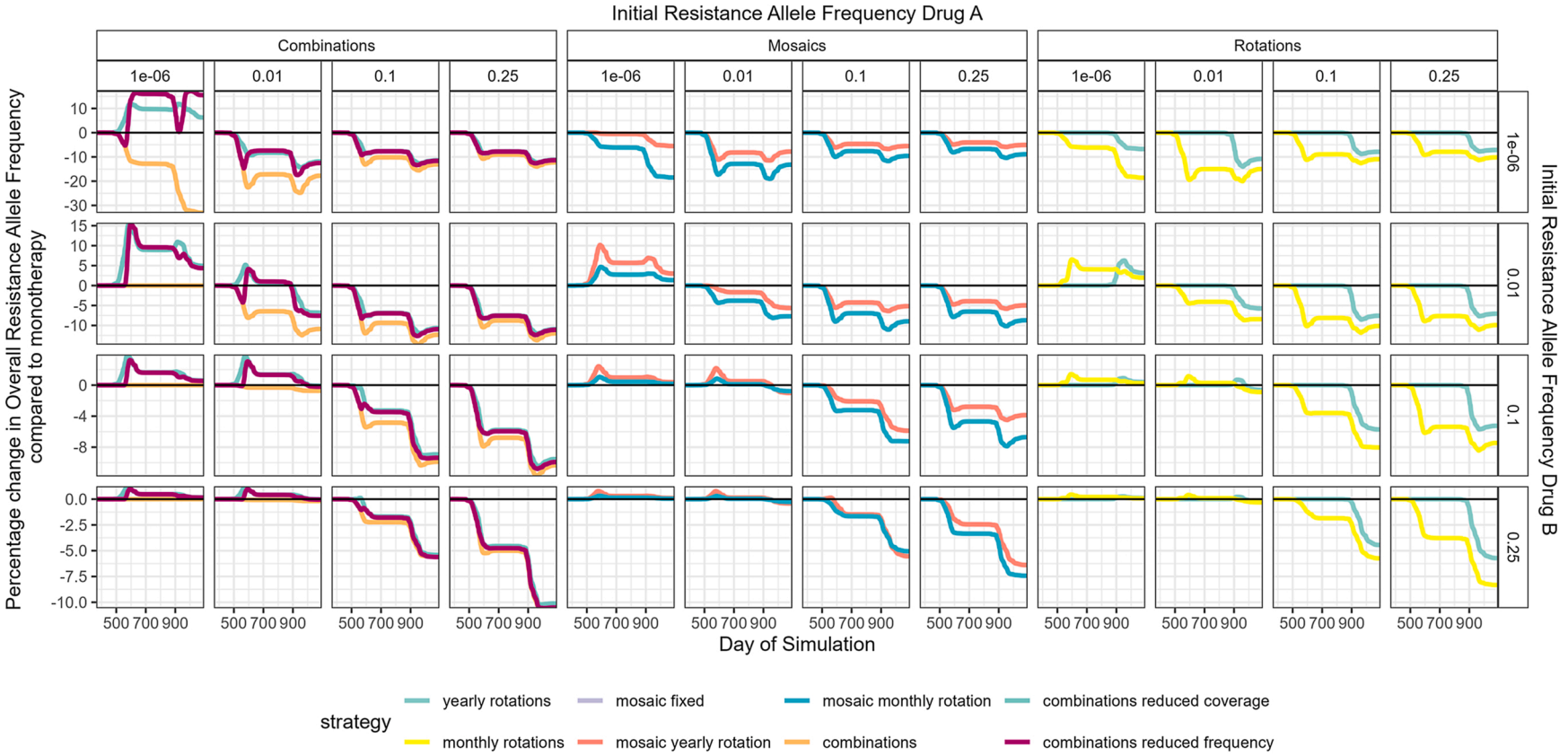


Fig. 6. Simulation Set 3 – Percentage Difference in the Resistance Allele Frequency Compared to Monotherapy. The y axis is the percentage difference, as calculated from Equation (1). Note, Drug 1 is the drug used in the monotherapy simulations, and Drug 2 is not deployed in the monotherapy simulations. The horizontal black line (at zero) represents the no difference between strategies. Values below the black line indicates the proposed strategy performed better, and values above performed worse than the Monotherapy comparator. The x-axis is the simulation day, and is restricted to not include the 1-year burn in which is the same across all strategies. Each line is the mean of 100 simulations, covering a range of geographic locations.

Under-dosing has two notable potential implications. The first is the impact on the evolution of resistance. The second is having an incorrect estimate of the resistance phenotype of the target population, as the reduced observed efficacy was due to under-dosing and not resistance. Whilst our simulations are agnostic to product, there is a need to further investigate the use of long-lasting formulations when used for targeting non-GIN parasites, such as moxidectin and sheep scab. It is critical that researchers and policy-makers utilising the same interventions communicate and coordinate their resistance management strategies, for example, SCOPS have consolidated quarantine recommendations for nematode and psoroptic mange control (Stubbings et al., 2020). The two-gene module (AR2) developed here allows for future exploration of the combined impacts of anthelmintic treatments applied for both GIN and ectoparasite control on the development of resistance.

One often highlighted component of ARM strategies is to maintain a "*refugia*" (Hodgkinson et al., 2019), where untreated livestock or pre-contaminated patches can act as a source of susceptible alleles. *Refugia* are anticipated to be beneficial for ARM when used in conjunction with combinations (Leathwick et al., 2012) and similarly with TST (Laurenson et al., 2013). A key aspect is considering what level of pasture contamination is needed to provide an effective *refugia*, and what level of pasture contamination is possible without allowing for rapid reinfection and the need to re-treat livestock. One of the current core tenets of resistance management is to reduce the usage of, and reliance on, anthelmintic treatments (Stubbings et al., 2020). Although a degree of reduced anthelmintic use and implementation of *refugia*-based strategies without production impacts is possible (Learmount et al., 2015), it is clearly important to note that this may come at the cost of increased transmission as the target GIN parasites may no longer be as effectively controlled, as was evident in our simulations considering reduced coverage and frequency of anthelmintic treatments (Fig. 5). This is consistent with industry messaging around using as little anthelmintic as possible to reduce AR selection but at the same time as much as necessary to control disease (Loeb, 2019). By moving livestock to contaminated patches to allow for reinfection, this increases the need for future treatments, which themselves provide further selection for resistance.

The challenge is to balance epidemiological goals, which are often short-term, with resistance management goals, which consider far longer time horizons, with no guarantee of pay-off, due to the inherent stochasticity of evolutionary processes. Previous modelling studies have identified potential tipping points whereby the benefit of reduced rate of development of resistance is offset by increased FEC (Berk et al., 2016) or increased economic costs (Pech et al., 2009) when considering reduced coverage and frequency of treatment. This is consistent with our simulations, which further suggest that dominance appears to be a far more important consideration than *refugia* in the absence of drug decay (Fig. 4). Interestingly, our simulations show that *refugia* is more important to consider when there are long tails of drug decay (Fig. 4); therefore guidelines for treatment may need to consider whether short course treatments are given, whether the drug is rapidly metabolised (and so the decay time is short), and whether in these circumstances universally treating all livestock may be preferable due to no appreciable resistance management benefit to offset the reduced clinical benefit.

When faced with the likely financial constraints of ARM strategies, e.g., combinations (due to their higher costs), the simulations presented here offer several options for further exploration. For example, from both a resistance management and parasite control (FEC reduction) aspect, it appears that reducing the coverage of anthelmintic treatments is preferable to reducing the frequency of treatments. Although we note we did not fully balance these two for equal financial cost. Furthermore, some options such as cohort mosaics are likely to be challenging to implement and did not appear to offer a resistance management benefit to offset this challenge (Fig. 5); especially when compared to combinations.

Mathematical models may well be able to identify the optimal pasture contamination, but a key question becomes, how robust does the *refugia* strategy become outside any optima, and more importantly, can optimally identified conditions be practically implemented by farmers? The design and implementation of resistance management strategies need to be robust even when implemented incorrectly, sub-optimally, or in the face of incomplete knowledge e.g., regarding the genetic basis of resistance (McIntyre et al., 2025). Ensuring strategies are implementable and robust regardless of variable conditions relating to the climatic/biological/operational nature of the system is a core consideration e.g. evaluation of SCOPS guidelines on focal farms (Learmount et al., 2016).

We would note three factors which we did not investigate but are widely considered important, being fitness costs, cross resistance and rotational grazing. For example, our presented simulations did not include fitness costs, despite "*A priori*, one expects such fitness cost" (Hodgkinson et al., 2019). Fitness costs are needed to maximise any benefit of *refugia.* Fitness costs are essentially always beneficial for any resistant management strategies, but strategies should not rely on them for effectiveness. When comparing combinations against rotations, fitness costs were found to be increase the favourability for combinations (Leathwick, 2013). Cross resistance is rarely included in models (REX Consortium, 2010). However in recent modelling of insecticide resistance which included cross resistance, this did not alter the choice between insecticide mixtures (equivalent to drug combinations) and rotations; remaining in favour of mixtures (Hobbs et al., 2023; Hobbs and Hastings, 2025b). Rotational grazing as a resistance management option is another consideration but would have to consider interactions with drug decay, treatment timing and parasite contamination levels between patches which would impact the performance of rotational grazing for resistance management.

Further to the above ARM robustness considerations, although broad economic evaluations of anthelmintic usage and AR have been made (Charlier et al., 2020), economic evaluations of ARM have been limited to a subset of treatment scenarios (e.g., drenching frequency and *refugia* size (Pech et al., 2009) and allied strategies such as grazing management (van der Voort et al., 2017)). The former identifies potential tipping points whereby the benefit of reduced rate of development of resistance is offset by the economic costs. This observation relates to the fact that scenarios that result in higher transmission (and the higher resulting FECs) may lead to production impacts and more treatments being required, and this would further select for resistance. This was not explored in the present study, although further model extensions to represent recommended FEC-based treatment decisions (Stubbings et al., 2020) would allow further quantification of the treatment costs of different ARM strategies against the rate of development of resistance.

In conclusion, the interventions we use to control and treat parasitic diseases are also those supplying the selection pressure for resistance and there is a need to balance treatment frequency with selection frequency. However, the need to treat is also dependent on the level of transmission, which itself can be minimised by effective treatment. Resistance management is inherently interwoven into parasite control, albeit often as an afterthought. Discussions of anthelmintic resistance management must simultaneously consider parasite transmission, pharmacology and genetics. We provide a simulation framework to enable such discussions allowing for a refinement into our understanding of parasite control in the presence of resistance evolution. We also provide quantitative output to infer dominance from coupled molecular studies of resistance frequency and FECRTs, to further aid ARM strategy applications.

CRediT authorship contribution statement

Neil Philip Hobbs: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **John Graham-Brown:** Writing – review &

editing, Supervision, Funding acquisition. **Eric R. Morgan:** Writing – review & editing, Methodology, Conceptualization. **Hannah Rose Vineer:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interests

The authors declare no competing interests.

Acknowledgements

We dedicate this manuscript in memory of Dr Dave Leathwick, whose substantial contributions to modelling anthelmintic resistance provided a foundation for our work. This work was funded by the Biotechnology and Biological Sciences Research Council, United Kingdom, project reference number: BB/X000923/1.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpddr.2026.100669.

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